RESPONSE

To Ms. Syoko Yamamura, Examiner of the Patent Office

1. Indication of International Application

PCT/JP03/03924

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4. Date of Notice 24.06.03

5. Contents of response

(1) In the Written Opinion dated June 24, 2003 (mailing date), the Examiner holds as follows by referring to the following Reference 1 and Reference 2:

Reference 1: FASEB Journal 13 (5 PART 2): pA907 March 15, 1999

Reference 2: JP 2001-037486 A (TANABE SEIYAKU Co., Ltd.) 2001.02.13

"Reference 1 describes a constitution for measuring the expression of H-FABP mRNA due to adriamycin during

cardiomyopathy. Reference 2 describes a constitution for measuring FABP at an mRNA level and a constitution for measuring using an anti-FABP antibody, and also describes human FABP as an FABP to be measured.

The invention of claims 1 to 18 does not have an inventive step over Reference 1 and Reference 2. Application of the method described in Reference 1 to the measurement of human H-FABP, and the constitution for measuring H-FABP using an anti-FABP antibody instead of the constitution for measuring the expression of mRNA can be easily performed by those skilled in the art."

The Applicant finds it difficult to agree with the Examiner's view as set forth above and would respectfully present the opinion as follows.

(2) The subject matter and characteristics of the present invention

(i) The present invention

The subject matter of the present invention in view of the definition of claims is as follows:

"1. A method for determining toxicity to the heart of an anthracycline-type anticancer chemotherapeutic agent, which comprises detecting human H-FABP in the blood separated from human.

2. The method of claim 1, wherein the detection of human H-FABP is performed by an immnochemical method using an antibody that recognizes human H-FABP.

3. The method of claim 2, wherein the immunochemical method is an enzyme immunochemical method, a latex agglutination assay or an immunochromatographic assay.

4. The method of claim 2, wherein the antibody is a monoclonal antibody.

5. The method of claim 1, wherein the anthracycline-type anticancer chemotherapeutic agent is adriamycin or daunorubicin hydrochloride.

6. A reagent for determining toxicity to the heart of an

anthracycline-type anticancer chemotherapeutic agent, which is used for performing the method of any of claims 1 to 5.

7. A reagent for determining toxicity to the heart of an anthracycline-type anticancer chemotherapeutic agent, which comprises an antibody that recognizes human H-FABP.

8. The reagent of claim 7, wherein the antibody is a monoclonal antibody.

9. The reagent of claim 7, wherein the anthracycline-type anticancer chemotherapeutic agent is adriamycin or daunorubicin hydrochloride.

10. A commercial package comprising the reagent of any of claims 7 to 9, and a written matter associated therewith, the written matter stating that said reagent can or should be used for determining toxicity to the heart of an anthracycline-type anticancer chemotherapeutic agent.

11. A kit for determining toxicity to the heart of an anthracycline-type anticancer chemotherapeutic agent, which comprises an antibody that recognizes human H-FABP.

12. The kit of claim 11, wherein the antibody is a monoclonal antibody.

13. The kit of claim 11, whrein the anthracycline-type anticancer chemotherapeutic agent is adriamycin or daunorubicin hydrochloride.

14. Use of an antibody that recognizes human H-FABP for determining toxicity to the heart of an anthracycline-type anticancer chemotherapeutic agent.

15. The use of claim 14, which comprises detecting human H-FABP in the blood separated from human.

16. The use of claim 15, wherein the detection of human H-FABP is performed by an enzyme immunochemical method, a latex agglutination assay or an immunochromatographic assay.

17. The use of claim 14, wherein the antibody is a monoclonal antibody.

18. The use of claim 14, wherein the anthracycline-type anticancer chemotherapeutic agent is adriamycin or daunorubicin

hydrochloride."

(ii) Characteristics of the present invention

The present invention relates to a method of determining the toxicity to the heart of an anthracycline-type anticancer chemotherapeutic agent, which comprises detecting human H-FABP separated from the blood of human, a reagent for the determination, which is used for performing the method, a commercial package containing the reagent for the determination, a kit containing an antibody recognizing human H-FABP, which is used for determining the toxicity to the heart of an anthracycline-type anticancer chemotherapeutic agent and use of the antibody.

Conventionally, the relationship between human H-FABP and the cardiotoxicity due to an anthracycline-type anticancer chemotherapeutic agent has not been known at all. Needless to say, it has not been known that human H-FABP in the blood separated from human can be an indicator of cardiotoxicity due to an anthracycline-type anticancer chemotherapeutic agent.

As is clear from the disclosure of the claims, the present invention has been completed based on the relationship between human H-FABP (particularly that in human blood) and cardiotoxicity due to an anthracycline-type anticancer chemotherapeutic agent.

(3) Contents of prior art

Reference 1: FASEB Journal 13 (5 PART 2): pA907 March 15, 1999

Reference 1 describes investigation of the effect of the administration of adriamycin on the expression of H-FABP in the heart cytoplasm. To be specific, it describes (i) the expression level of H-FABP mRNA in the heart cytoplasm of rat administered with adriamycin decreased to 1/4 of the level of control group administered with saline, and (ii) the decreased expression level of H-FABP mRNA recovers by the administration of L-Carnitine, which is one kind of amino acid.

Reference 2: JP 2001-037486 A (TANABE SEIYAKU Co., Ltd.) 2001.02.13

Reference 2 describes the finding that a drug that enhances the expression of FABP can be a therapeutic agent for nephropathy. In addition, Reference 2 describes a screening method based on this finding, or, a screening method for a therapeutic agent for nephropathy, which comprises assaying the action of a test substance on the enhancement of FABP expression in animal cells. Furthermore, it describes, as a method of detecting the enhancement of FABP expression, a method comprising detecting FABP mRNA and a method comprising detecting FABP protein using an anti-FABP antibody.

(4) Comparison of the present invention and cited invention

As described in detail in the following 1 to 4, the constitution of the present invention cannot be easily conceived by those skilled in the art from the disclosure of Reference 1 and Reference 2.

1. Relationship between H-FABP and cardiotoxicity due to an anthracycline-type anticancer chemotherapeutic agent

Reference 1 describes an experimental fact that the expression level of H-FABP mRNA in the heart cytoplasm of rat administered with adriamycin decreased to 1/4 of the level of control group administered with saline. Therefore, Reference 1 is understood as describing the relationship between the expression level of H-FABP and an anthracycline-type anticancer chemotherapeutic agent.

However, Reference 1 does not describe or suggest the relationship between human H-FABP and cardiotoxicity due to an anthracycline-type anticancer chemotherapeutic agent, namely, that human H-FABP can be an indicator of cardiotoxicity due to an anthracycline-type anticancer chemotherapeutic agent. What is disclosed by Reference 1 is solely the fact that

administration of adriamycin results in the fluctuation (decrease) of the level of H-FABP expression, and the relationship between such fluctuation (decrease) and the cardiotoxicity has not been described or suggested. Please note that all of claims 1 to 18 of the present application have been specified by the constitution of "human H-FABP", "determination of cardiotoxicity due to an anthracycline-type anticancer chemotherapeutic agent", and therefore, the difference from the invention disclosed in Reference 1 is clear.

Moreover, Reference 2 simply describes an invention having a completely different constitution from that of the present invention. Thus, it is clear that the present invention completed taking note of the relationship between human H-FABP and cardiotoxicity due to an anthracycline-type anticancer chemotherapeutic agent is not suggested by the combination of Reference 1 and Reference 2, let alone Reference 2 by itself.

From the foregoing, we conclude that the present invention cannot be easily conceived by those skilled in the art from the description of Reference 1 and Reference 2.

As described in detail under 1. above, the present invention clearly cannot be conceived easily by those skilled in the art from Reference 1 and Reference 2. We would additionally note that the present invention is further different from the inventions disclosed in Reference 1 and Reference 2 in the following points 2, 3 and 4, and due to such difference, those skilled in the art have utmost difficulty in conceiving the present invention.

2. Tissue (sample) for measurement of H-FABP

Reference 1 describes an experimental fact that the expression level of H-FABP mRNA in the heart cytoplasm of rat administered with adriamycin decreased to 1/4 of the level of control group. On the other hand, the present invention is characterized by detection of human H-FABP in the blood

separated from human. Therefore, while the tissue (sample) to be the H-FABP measurement target in Reference 1 is heart cytoplasm (H-FABP expressed tissue), the tissue (sample) to be the measurement target is blood in the present invention.

Please note that even those skilled in the art cannot easily conceive the present invention characterized by detection of H-FABP in blood, from the disclosure of Reference 1 having such difference. This is because even those skilled in the art cannot anticipate that, in a human expressing cardiotoxicity due to an anthracycline-type anticancer chemotherapeutic agent, H-FABP flown from the heart cell is detected in the peripheral blood, which is not a direct expression tissue of H-FABP, and that the amount of flow of H-FABP is correlated with the cardiotoxicity due to an anthracycline-type anticancer chemotherapeutic agent.

Reference 2 merely describes an invention having a completely different constitution from that of the present invention. Thus, it is clear that the present invention characterized by detection of H-FABP in the blood for the determination of cardiotoxicity due to an anthracycline-type anticancer chemotherapeutic agent is not suggested by the combination of Reference 1 and Reference 2, let alone Reference 2 by itself.

From the foregoing, we conclude that, as is clear from the above paragraphs 1. and 2., the present invention cannot be easily conceived by those skilled in the art based on the description of Reference 1 and Reference 2.

3. Expression level of H-FABP

Reference 1 describes an experimental fact that the expression level of H-FABP mRNA in the heart cytoplasm of rat administered with adriamycin decreased to 1/4 of the level of control group. Therefore, the detection in the description of Reference 1 means detection of a decrease in H-FABP in the adriamycin administration group as compared to the control

group.

In contrast, the "detection" in the present invention means detection of an increase in H-FABP in patients expressing cardiotoxicity due to an anthracycline-type anticancer chemotherapeutic agent as compared to H-FABP of healthy volunteers [see, for example, the present specification, page 8, lines 21-26 (page 10, lines 11-19 in English version)]. Therefore, the description of Reference 1 does not teach the present invention characterized by the detection of increase in H-FABP, but rather prevents the idea of the present invention.

Reference 2 merely describes an invention having a completely different constitution from that of the present invention. Thus, it is clear that the present invention is not suggested at all by the combination of Reference 1 and Reference 2, let alone Reference 2 by itself.

From the foregoing, we conclude that, even based on this paragraph 3. alone, the present invention cannot be easily conceived by those skilled in the art based on the description of Reference 1 and Reference 2.

4 Difference between human and rat

Reference 1 discloses the experimental results obtained using rat as a test animal. Therefore, the experimental results exclusively concern rat.

However, in view of the species difference in the toxicity of drugs, it is a technical common knowledge in the pertinent field that the finding obtained using rat cannot be necessarily applied directly to human. In general terms, moreover, to obtain clear experimental results, drugs are administered at high doses in animal experiments, where the dose does not reflect the dose to human in clinical use in most cases. Consequently, the presence of a specific phenomenon observed upon administration of a certain dose (particularly high dose) to a test animal does not necessarily promise occurrence of a similar phenomenon in human at a dose employed

in clinical situations. The likelihood is predominantly higher that, combined with factors such as species difference and the like, such phenomenon is not observed, which is a well-known fact. As explained above, i) due to the species difference between human and rat, the toxicity in human cannot be always predicted from the experiment with rat, and ii) the results of drug administration in test animal (where any experimental dose can be set and the dose is not particularly limited) do not reflect the results of drug administration in human (where clinical dose is limited to a defined range). Therefore, it would be appreciated that Reference 1 does not teach any results in human administered with adriamycin.

In contrast, inasmuch as the present invention has been completed based on the results obtained from cancer patients administered with adriamycin, as described in Example 1, the present invention is clearly useful for the determination of cardiotoxicity in human, namely, actual patients (administered with doses employed in clinical situations). To clarify this aspect, the present invention has been specified for human as a subject by the constitution defined by "separated from human···" (e.g., Claim 1), "an antibody that recognizes human H-FABP" (e.g., Claim 7) and the like, and the characteristics have been specifically reflected in the invention relating to the steps of the method of the present invention (e.g., "detecting human H-FABP in the blood separated from human ···" in Claim 1).

Furthermore, Reference 2 merely describes an invention having a completely different constitution from that of the present invention. Thus, it is clear that the present invention is not suggested at all by the combination of Reference 1 and Reference 2, let alone Reference 2 by itself.

From the foregoing, we conclude that, even based on this paragraph 4. alone, the present invention cannot be easily conceived by those skilled in the art based on the description of Reference 1 and Reference 2.

(5) Conclusion

We believe that the inventive step of the present invention over Reference 1 and Reference 2 should be fully appreciated from the foregoing detailed explanation.